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Intermolecular Phosphite-Mediated Radical Desulfurative Alkene Alkylation Using Thiols

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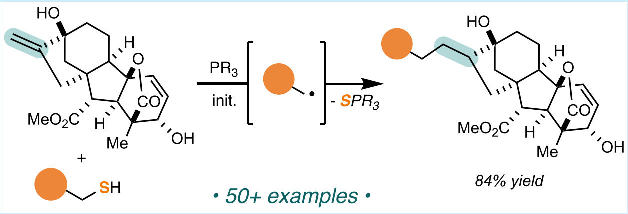
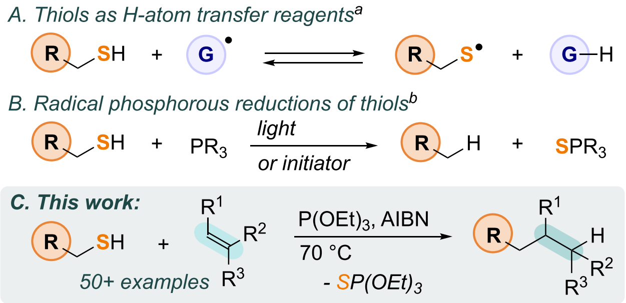
Supporting Information

ABSTRACT: We report herein the development of a S atom transfer process using triethyl phosphite as the S atom acceptor that allows thiols to serve as precursors of C-centered radicals. A range of functionalized and electronically unbiased alkenes including those containing common heteroatom-based functional groups readily participate in this reductive coupling. This process is driven by the exchange of relatively weak S−H and C−S bonds of aliphatic thiols for C−H, C−C, and S−P bonds of the products formed.



Renewed enthusiasm surrounding the ability of open-shell intermediates to forge carbon frameworks has spurred the development of new methods of accessing C-centered radicals.[1] Sulfur-based reagents have been developed for C−C bond construction via polar processes[2] and radical substitutions.[3] Xanthate-based reductive alkylation[4] presents the most general method for radical-based C−C bond construction, though this does require xanthate removal with a discrete synthetic step and an excess of H atom donor such as *n*-tributyltin hydride, tris(trimethylsilyl)silane, hydrophosphorous acid, or 2-propanol is generally needed.[5] Thiyl radicals, themselves valuable H atom transfer reagents (Scheme 1A),[6] are commonly generated via disulfide bond cleavage or H atom abstraction and undergo reversible addition to π-systems. As a result, thiols have become a mainstay of many radical-mediated processes. Despite this ubiquity, thiols have been relegated to essentially one role: a source of S-centered radicals.[7]

Scheme 1. Atom-Transfer Reactivity of Thiols



[a]See ref 6. [b]See refs 8−11.

Walling and Hoffman were among the first to report that alkyl thiols were cleanly reduced to the corresponding alkanes using UV light or thermal initiators and triethyl phosphite via the intermediacy of a C-centered radical from cleavage of the C−S bond (Scheme 1B).[8,9] Subsequently, radical thiol desulfurization via S atom transfer to phosphorus-based reagents was reported using thermal[10] and photochemical conditions.[11] Minozzi and Nanni reported that alkene alkylations could be achieved through a *tert*-butyl isocyanide induced thiol desulfurization and interception of the C-centered radical intermediate with an alkene.[12] This work outlined three thiols that were successful alkylating agents for four electron-rich vinyl ethers and vinyl silanes.[13] Hashmi and co-workers recently reported a photochemical, Au-catalyzed reductive C−C coupling using thiols and vinyl arenes.[14] Despite these developments, radical-mediated methods for C−C bond formation using thiols remain limited.[15]

We recently reported a regioselective O atom transfer enabled alkene hydroamination using *N*-hydroxyphthalimide as both the H atom and phthalimide sources.[16,17] Considering the thermodynamics that propel that process—relatively weak N−O and O−H bonds exchanged for stronger C−N, C−H, and O−P bonds—we hypothesized that thiols could analogously serve as alkyl and H atom sources when paired with an S atom accepting phosphite under mild reaction conditions.[18] Application of this strategy would provide an orthogonal role for thiols in synthetic radical chemistry as alkylating agents and provide a transition-metal-free alternative to radical-mediated reductive alkene alkylations.[19,20]

We began our investigations by subjecting 2-mercaptoacetanisole (**1**)[21] and *n*-butyl vinyl ether (NBVE, 1.5 equiv) to a small excess of triethyl phosphite (1.5 equiv) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 0.15 equiv) in benzene for 12 h at 70 °C. The desired desulfurized alkylation product, **2a**, was isolated in 42% yield alongside 50% yield of the

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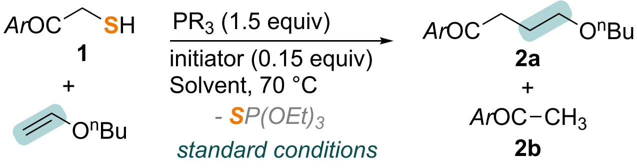
unwanted thiol reduction product, **2b** (Table 1, entry 1). Assessment of a range of other phosphites and phosphines produced similar or less efficient results.[22] Similarly, replacing AIBN with other thermal radical initiators diminished the yield of **2a**. In the absence of either triethyl phosphite or AIBN, **2a** was not detected (entries 2 and 3, respectively) confirming their necessity in the observed radical desulfurative alkylation. Notably, thiol−ene reaction products resulting from thiyl radical addition to alkenes throughout these studies were not observed.[23]

Table 1. Desulfurative Alkylation Reaction Conditions[a]



entry	deviation from standard conditions	yield of **2a**[b] (%)
1	none	42 (50% **2b**)
2	no $P(OEt)_3$	nd
3	no AIBN	nd
4	**1** added over 2 h	80 (8% **2b**)
5	**1** added over 7.5 h[c]	93 (7% **2b**)

[a] Reactions carried out with **1** (1 equiv), $P(OEt)_3$ (1.5 equiv), *n*-butyl vinyl ether (1.5 equiv), and AIBN (0.15 equiv) in 0.1 M degassed benzene at 70 °C for 14 h; Ar = 4-OMe(C_6H_4); nd = not detected. [b] Yields are of isolated material following purification via silica gel chromatography. [c] A 0.16 M solution of **1** in benzene was added at a rate of 2.3 μL/min.

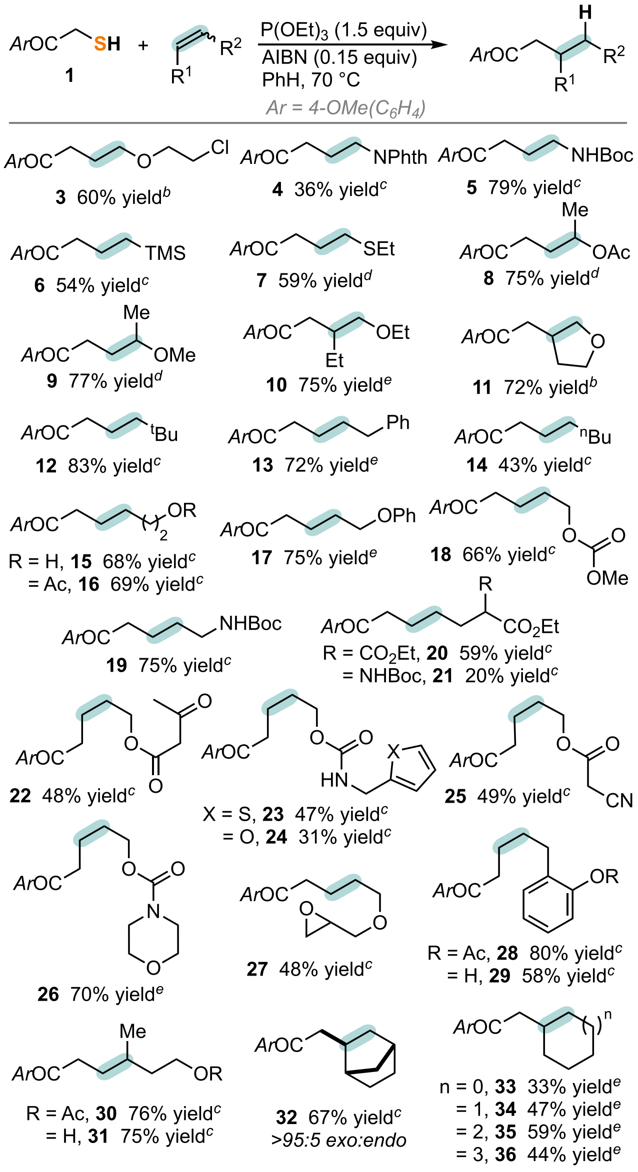
Observing a suboptimal ratio of **2a**:**2b** regardless of the phosphorus reagent, solvent, or initiator used, we hypothesized that **2b** was formed via competitive H atom transfer from the thiol starting material to the intermediately formed C-centered radical prior to olefin addition.

To promote olefin addition without increasing the equivalents used, we opted to keep the concentration of thiol low with respect to alkene by adding the thiol to the reaction mixture over time. Adding a benzene solution of **1** and AIBN via syringe pump to the remaining reaction components over 2 h improved the selectively for **2a** production (80% yield, entry 4). Decreasing the rate of addition so that **1**/AIBN was added over 7.5 h resulted in the isolation of **2a** in 93% yield (entry 5), while decreasing the rate of addition further failed to provide additional benefits.

We then investigated the scope of alkenes that participated in this radical desfulfurative alkylation using **1** as a model thiol (Scheme 2). An array of functionalized alkenes containing an alkyl chloride (**3**), protected N-based groups (**4** and **5**), silyl (**6**), thioether (**7**), and vinyl ethers (**8−11**) underwent desulfurative alkylation with moderate to excellent efficiencies. Electronically unbiased alkenes such as *tert*-butyl ethylene (**12**), allyl benzene (**13**), and 1-hexene (**14**) were also easily alkylated to exclusively give the linear products. Attempts at analogously alkylating styrene were unsuccessful, resulting in mixtures of unidentified oligomers.

Alkenes with pendant functionality were also evaluated. 3-Buten-1-ol was reductively alkylated with **1** in nearly identical efficiency whether the primary alcohol was protected as an acetate (**16**, 69% yield) or not (**15**, 68% yield). Phenyl ether (**17**), alkyl carbonate (**18**), carbamate protected 1° amine (**19** and **21**), and ester (**20**) groups were also well tolerated. Olefins in the presence of base sensitive β-keto ester (**22**) and nitrile (**25**) groups, as well as heterocycles such as thiophene (**23**), furan (**24**), and morpholine (**26**), were successfully alkylated using **1** and triethyl phosphite.

Scheme 2. Alkene Scope[a]



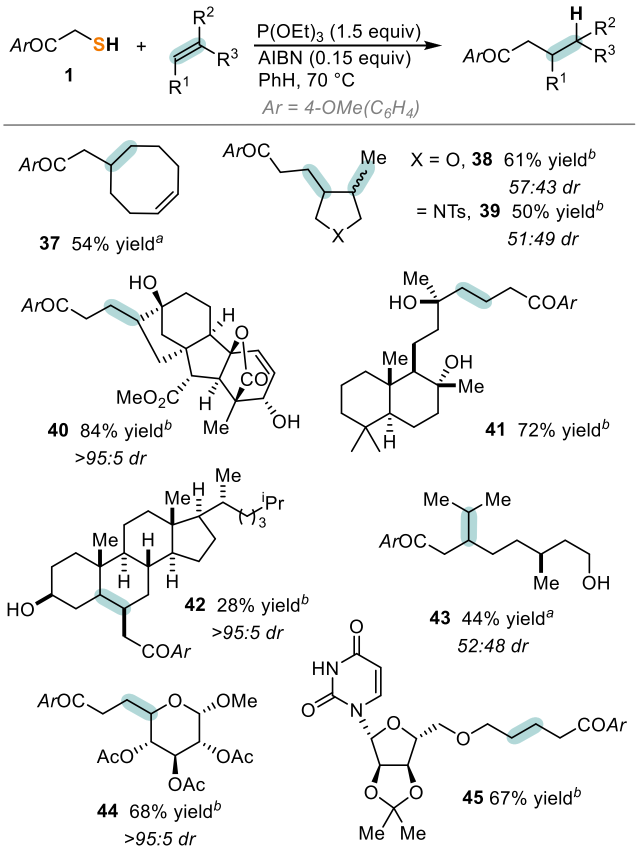
[a] All reactions carried out using **1** (1 equiv), $P(OEt)_3$ (1.5 equiv), AIBN (0.15 equiv), and alkene in benzene at 70 °C by adding **1** via syringe pump over 7.5 h followed by continued heating for an additional 6 h; yields are of isolated material following chromatography on silica gel. Diastereomeric ratios determined by analysis of crude reaction mixtures by ^{1}H NMR with the structure of the major diastereomer shown. Phth = phthalimidyl, Boc = *tert*-butyl carbamoyl, TMS = trimethylsilyl, Ac = acetyl, Ts = *p*-tolylsulfonyl. [b] Using 1.5 equiv of alkene. [c] Using 5 equiv of alkene. [d] Using 3 equiv of alkene. [e] Using 10 equiv of alkene.

Notably, an epoxide-containing allyl ether resulted in the formation of the desired reductive alkylation product **27** in 48% yield with no observed epoxide degradation despite the reducing ability of phosphites.[24] We observed diminished reaction efficiency in the presence of a phenol (**29** in 58%) as compared to its acetyl protected analogue (**28** in 80% yield).[25]

Similar to the case of 3-buten-1-ol, geminal disubstituted alkene, 3-methylbut-2-en-1-ol (**31**) and its acetylated congener (**30**) were alkylated with essentially the same efficiencies (76% and 75% yields, respectively). Cyclic alkenes were alkylated with good reaction efficiencies (**32**−**36**) with norbornene being the most efficient likely due to the release of ring strain upon addition.

Cyclic diene, 1,5-*cis*,*cis*-cyclooctadiene, underwent reductive alkylation to produce **37** in 54% yield without observation of the bicyclic product arising from intramolecular cyclization (Scheme 3). Subjecting diallyl ether and *N*,*N*-diallyl tosylamine to our standard reaction conditions resulted in the formation of each of the alkylated, cyclized products **38** (61% yield) and **39** (50% yield), respectively. We did not observe alkylation products for either of these 1,6-heptadienes without cyclization. This agrees with the rate of cyclization in 1,5-*cis*,*cis*-cyclooctadiene (~1 × 10^5 s^{-1})[26] being slower than H atom transfer from alkyl thiols to C-centered radicals (4 × 10^6 to 2 × 10^7 s^{-1})[27] but 5-*exo*-trig cyclization being faster (~9 × 10^8 s^{-1})[26] in 1,6-heptadienes.

Scheme 3. Alkenes in Complex Molecules Undergo Reductive Alkylation*

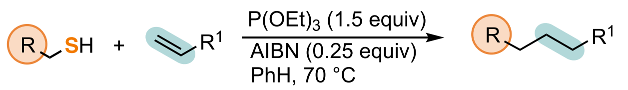


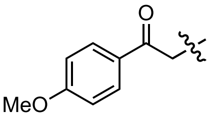
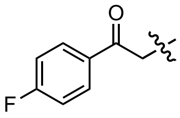
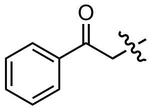
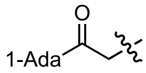
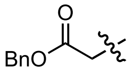
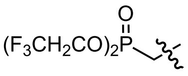
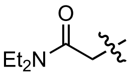
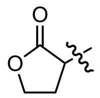
[*] All reactions were carried out using the conditions outlined in Scheme 2; yields are of isolated material following chromatography on silica gel; diastereomeric ratios determined by analysis of crude reaction mixtures by ^{1}H NMR with the major diastereomer shown. Ac = acetyl, Ts = *p*-tolylsulfonyl. [a]Using 10 equiv of alkene. [b]Using 5 equiv of alkene.

We next turned our attention to more complex, alkene-containing compounds (Scheme 3). The methyl ester of gibberellic acid underwent chemoselective reductive alkylation with **1** at the geminal alkene with high reaction efficiency (**40** in 84% yield) without indication of alkene alkylation of the 1,2-disubstituted allylic alcohol.[28] Naturally occurring bicyclic diterpene, sclareol, was converted to **41** in 72% yield. Alkylated cholesterol (**42**) and (−)-citronellol (**43**) provide two examples of trisubstituted alkenes contained within functionalized frameworks that successfully participated in this process. A vinyl enol ether derivative of D-(+)-glucose was successfully alkylated using **1**, producing **44** in 68% yield with no evidence of unwanted epimerization as was a 5′-*O*-allyl uridine nucleoside derivative (**45** in 67% yield).

We then focused on assessing the variety of thiols that could serve as alkylating agents in this desulfurative process (Table 2). We elected to conduct this thiol survey using NBVE and

Table 2. Scope of Thiols That Serve as Alkylating Agents[a]



Entry	R	R^1	
		= O^{n}Bu	= ^{t}Bu
1		**2a** 93% yield	**12** 83% yield
2		**46a** 94% yield	**46b** 45% yield
3		**47a** 96% yield	**47b** 43% yield
4		**48a** 98% yield	**48b** 75% yield
5		**49a** 68% yield	**49b** 52% yield
6		**50a** 60% yield	**50b** 55% yield
7		**51a** 47% yield	**51b** 40% yield
8		**52a** 32% yield[b]	**52b** 30% yield

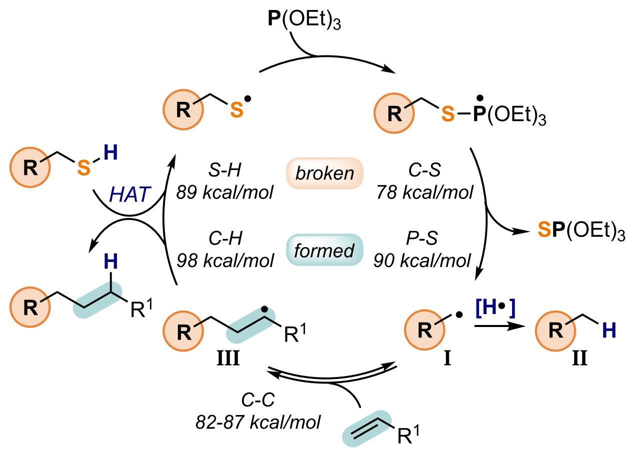
[a] All reactions were carried out using the conditions outlined in Scheme 2; yields are for isolated material following chromatography on silica gel. 1-Ada = 1-adamantyl. [b]Carried out using 5 equiv of alkene.

tert-butyl ethylene as model alkenes because of their favorable spectroscopic and physical properties. While our model thiol, **1**, featuring a 4-methoxyaryl ketone motif efficiently afforded the reductive alkylation of both model alkenes (entry 1, compounds **2a** and **12**), reaction efficiencies were only moderately influenced when the methoxy group was replaced with either an H or F atom (entries 2 and 3, compounds **46a,b** and **47a,b**). The primary thiol derived from 1-adamantyl methyl ketone also resulted in excellent reaction efficiencies with NBVE and *tert*-butyl ethylene (entry 4, compounds **48a,b**).

Thiols derived from a benzyl ester, trifluoroethyl phosphonate ester, and amide also proved capable alkylating agents in this S atom transfer alkylation process (entries 5−7, compounds **49a,b**, **50a,b**, and **51a,b**) allowing installation of synthetically valuable functional handles in the product. The secondary thiol derived from γ-butyrolactone also successfully produced the desired alkylation products from both model alkenes used albeit with decreased efficiency (entry 8, compounds **52a,b**).

A mechanistic proposal in line with our experimental results is provided in Scheme 4. Thermal radical initiation followed by H atom abstraction from thiol produces the corresponding thiyl radical, which undergoes addition to triethyl phosphite.[8] This thiyl phosphite adduct then undergoes rapid and preferential β-cleavage of the C−S bond, forming triethyl phosphorothioate and C-centered radical **I**. We observed that with high relative concentrations of thiol this C-centered radical abstracts a H atom from the thiol starting material, resulting in alkane **II**; maintaining low relative concentrations of thiol through slow addition, **I** undergoes regioselective alkene addition resulting in 2° or 3° C-centered radical, **III**. Radical **III** can now serve as the H atom abstraction agent to deliver the desired alkylation product and regenerate the thiyl radical. This process is driven by the cleavage of relatively weak S−H and C−S bonds of the starting materials (∼89 and 78 kcal/mol, respectively) to form stronger P−S, C−C, and C−H bonds of the products (90, ∼85, 98 kcal/mol).[29]

Scheme 4. Mechanistic Proposal



In conclusion, we describe a S atom transfer, phosphite-mediated reductive alkylation of a wide range of alkenes, including examples of those present in naturally occurring, biologically active compounds, using thiols as C-centered radical precursors. We demonstrate that a variety of 1° and 2° thiols adjacent to anion stabilizing groups serve as precursors to achieve C−C bond formation with olefins. This expands the ability of thiols in radical-mediated processes and opens orthogonal pathways in strategic synthetic planning.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03018.

Full experimental details and characterization data including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.
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